AN AUTOPSY SERIES ON FATAL PULMONARY EMBOLISM AT GRACE-NEW HAVEN HOSPITAL, WITH EXPERIMENTAL WORK ON THE PRODUCTION AND REMOVAL OF PULMONARY EMBOLI IN DOGS

Harry Charles Miller Jr.

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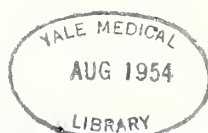

By

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AN AUTOPSY SERIES ON FATAL PULMONARY EMBOLISM AT GRACE-
NEW HAVEN HOSPITAL, WITH EXPERIMENTAL WORK ON THE
PRODUCTION AND REMOVAL OF PULMONARY EMBOLI IN DOGS.

Purpose.

The purpose of this study is to investigate the
occurrence of fatal pulmonary embolism in patients coming
to autopsy in the New Haven Hospital during the eighteen
year period from 1935 to 1953, inclusive; and to explore
briefly the historical, clinical, and experimental basis
for the attempt to remove surgically emboli from the
pulmonary artery (Trendelenberg Operation).

Introduction.

During the past 50 - 75 years the natural course of
many diseases has been significantly altered. If outright
cure has not been achieved, palliation can now be offerred
to patients which prolongs life, and may make terminal
phases more comfortable. Many processes which in the past
terrorized physicians and patients alike are now considered
to be acceptable.

The subject of this paper is an exception to this
general trend of progress. Massive pulmonary embolism still
carries as grave a prognosis now, as at any time in the past,
for those affected. A major step forward in the past half-
century in the management of new thromboembolic disease has

been the development of the anticoagulants. The value of
these in preventing emboli to the pulmonary system, parti-
cularly from the peripheral veins, is now fairly well
established. In a sizeable group of patients Allen (1)
reported one postoperative death due to pulmonary embolism
in 1500 cases who had been placed on heparin prophylacti-
cally; the expected rate in this group was 86/1500.
Bauer (2) in 1946 reported a mortality rate of 18% in
patients with thrombophlebitis not treated with heparin,
as compared with 1.4% in a similar group of patients treated
with heparin. Debakey in his recent review of the world
literature can find no evidence that the advent of this is the
case (41). This is a remarkable revelation. Certainly some
lives --- probably a great many --- have been saved by the
judicious use of anticoagulants in the prophylaxis and
treatment of thromboembolic disease. Undoubtedly as the
broad vista of surgery ever becomes wider to encompass disease
which has attacked the old and infirm, the incidence of
thromboembolic disease can be expected to be ever on the
increase.

However, for the patient who, postoperatively or other-
wise, develops a pulmonary embolus there is little that can
be done for him now that was not available many years ago.
This is true despite the fact that many men in the United
States and Europe have striven for years to develop satis-
factory techniques for the treatment of the embolism, both
by surgical and medical means. Part of this paper will

deal with the incidence and certain other characteristics
of fatal pulmonary embolism occurring in the New Haven
Hospital, and part will be concerned with a preliminary
report on a surgical method of attacking the problem.
The need for such a study would seem to evident when it is
seen that gross pulmonary emboli are found at approximately
5% of all autopsies.

The Autopsy Series

Material.

The patients included in this study were a series of
6529 consecutive autopsies from the New Haven Hospital
during the period from March 10, 1935 to March 12, 1953.
This series constitutes a representative sampling of the
general population of this section, since this institution
in a general county hospital serving about 300,000 persons in
the Greater New Haven area, admitting all types of patients
without emphasis on any particular age group, socio-economic
status, sex or racial distribution, or disease process.
Autopsies are obtained on every patient possible, the 1952
total being 46% of all patients dying in the hospital.
Also included in this series are a few autopsies done at the
hospital on patients dying outside the hospital but sent by
their family doctor for post-mortem examination.

From this series of 6529 autopsies a detailed study was
made of all those showing pulmonary emboli, regardless of

size or influence on the patient's course. This group was further subdivided into those receiving so-called "fatal" pulmonary emboli. This latter classification was given to those emboli which were considered to be the actual cause of death to the patient. Since in a poor-risk patient a very small embolus may be the precipitating factor in causing the death, an arbitrary limit was set on the size of the embolus and/or infarct to be labelled "fatal". The smallest embolus regarded to be the direct cause of death in this series was sufficiently large to occlude a lobar artery or larger artery completely. Smaller emboli were included in the group of "pulmonary emboli" but not in the group of "fatal pulmonary emboli".

The findings at autopsy in these patients were studied from several standpoints. The age and sex of the patient, the hospital service, the length of hospital stay, and the duration of bed rest. The primary disease or reason for admission was categorized as either metabolic, infectious, postoperative, posttraumatic, neoplastic, or none. It was attempted to learn what prophylactic measures, if any, were utilized, but this was difficult to determine in most instances. It was noted whether there was a diagnosis of pulmonary embolism and/or thrombophlebitis made during the hospital stay, and what other diagnoses were considered to account for the embolic episode. Previous pulmonary emboli were noted, as was any therapy for either the emboli or the thrombophlebitis. An attempt was made to classify the symptoms shown referrable

to the embolic episodes, and especially the terminal symptoms. In the postmortem reports the site of embolus lodgement was noted, the presence of pleural fluid, the findings of thrombophlebitis or mural thrombi, and finally, an attempt was also made to determine the length of survival following the fatal pulmonary embolism.

Results

Most of the following tables and diagrams are self-explanatory; in the case of those which are not, a short description is given.

1. Incidence.

Incidence of <u>all</u> pulmonary emboli in total series:
$$290/6529 = 4.44\%$$

Incidence of <u>fatal</u> pulmonary emboli in total series:
$$67/6529 = 1.025\%$$

Incidence of <u>fatal</u> pulmonary emboli in series of <u>all</u> pulmonary emboli: $67/290 = 23.10\%$

Incidence in 5-year periods:

	3/1935-3/40	3/40-3/45	3/45-3/50	3/50-3/53 (3 yr)
# of Aut.	1546	1800	2015	1186
# Pul. Emb. (all)	84	72	87	47
(%)	5.44%	3.83%	4.32%	3.96%
# Fatal Pul. Emb.	21	12	18	16
(%)	1.42%	0.64%	0.89%	1.35%
Fatal PE/All PE	25.0%	16.6%	20.7%	34.1%

Distribution as to Hospital Service:

Medical   .... $40/67 = 59.7\%$

Surgical   .... $19/67 = 28.4\%$

Obstetric   .... $2/67 = 2.9\%$

Psychiatric.......... $3/67 = 4.5\%$

Outside   .... $3/67 = 4.5\%$

The overall presence of pulmonary emboli in a general autopsy series is almost 5%, the high mortality rate among all pulmonary emboli reflecting the concern of the patient afflicted and of the physician treating him. Perhaps explainable, but still surprising, is the high mortality rate from pulmonary embolus over the past three years, being twice that ten years ago and 50% higher than that five years ago. While pulmonary emboli are usually thought of as surgical problems, the overwhelming preponderance of fatal emboli to the lung on the medical services reflects the concern of the surgical staffs for the problem and the possibly inherently poorer condition of the bed-ridden medical patient.

2. Age.

0-9 yrs	10-19	20-29	30-39	40-49	50-59	60-69	70 plus
X	X	X	X	X	X	X	X
			X	X	X	X	X
1.5%	1.5%	1.5%		X	X	X	X
			7.5%	X	X	X	X
				17.9%	X	X	X
					X	X	X
					X	X	22.4%
					23.9%	23.9%	

3. Sex.

Males 41 (61.1%) : Females 26 (38.9%)

4. Primary Disease Process.

a. Metabolic (including arteriosclerosis, chronic rheumatic heart disease, etc.) 24 (35.9%)

b. Infectious (acute rheumatic heart disease, pneumonia, etc.) 13 (19.4%)

    c.   Surgical (postoperative, obstetric, etc.) 21 (31.4%)

    d.   Neoplastic without operation   6 (8.9%)

    e.   None   3 (4.5%)

5. Prophylaxis.

    None 66 (98.5%)

    Heparin 1 (1.49%)

6. Diagnosis clinically of embolic episodes.

    a. of thrombophlebitis   21 (31.4%)

    b. of pulmonary embolus   23 (34.3%)

    (In these two categories there is considerable overlap).

    c. other:

        1)   myocardial infarct   11 (16.4%)

        2)   pneumonia   12 (17.9%)

        3)   congestive failure   5 (7.4%)

        4)   other diagnoses   15 (22.4%)

7. Therapy

    a. of thrombophlebitis:

    "Paevex"........................ 1

    Digitalis and Diuretics....... 2

    Anticoagulants................. 4

    b. of pulmonary embolus:

    chest strapped.................. 1

    Digitalis...................... 9

    Oxygen.........................15

    Antibiotics.................... 6

    Morphine sulfate.............. 2

(Two patients received 50mgm vitamin K each day stopping 3-4 days before death).

8. Duration of life after pulmonary embolus (fatal):

Sudden death 18 (26.9%)

  0 - 10 minutes 1 (1.5%)

11 - 60 minutes 8 (11.9%)

  1 - 10 hours 12 (17.9%)

11 - 24 hours 6 (8.9%)

More than one day 17 (25.4%)

Unknown or found dead 5 (7.5%)

In this series it is seen that about 35% of the patients died within the first 10 minutes, and about 48% within the first hour.

9. Signs and Symptoms.

  a. of pulmonary emboli in general:

    dyspnea 58.2%

    rales 52.3%

    cyanosis 50.7%

    dullness 34.3%

    fall in blood pressure 32.9%

    increased temperature 28.4%

    increased pulse 28.4%

    chest pain 23.9%

    hemoptysis 22.4%

    increased respiration 19.4%

    leg pain 17.9%

    coma 13.4%

    cough 8.9%

b. of terminal event:

cyanosis 34.3%

dyspnea 31.4%

fall in blood pressure 22.4%

rales 16.4%

increased PRT 16.4%

coma 13.4%

pain 8.9%

Then, hemoptysis, sweating, cessation of respirations.

Others or none 19.4%

10. Previous Pulmonary Embolic Episodes.

None 23 (34.3%)

One 7 (10.4%)

Several 37 (55.3%)

11. Post-mortem findings.

a. Location of pulmonary embolus at autopsy:

Massive (in pulmonary outflow tract, occluding
pulmonary valve, or occluding main pulmonary
arterial trunk itself)   17 (25.4%)

Primary (occluding either or both right or left
main pulmonary arteries)   29 (43.3%)

Secondary (occluding one or more main lobar
arteries to either or both lungs)   21 (31.3%)

Right 8

Left 3

Both 10

b. Presence of pleural fluid:

  None noted at autopsy 23

  0-100 cc total   8

  101-500 cc total   13

  501 plus total · 16

  Unknown   7

c. Probable site of thrombophlebitis:

  None found at autopsy 14

  Peripheral veins   53

    Inf. Vena Cava   2

    Iliacs   6

    Femorals   21

    Popliteals   7

    Pelvic veins   6

    Multiple veins   11

  Cardiac mural thrombi 25

  Both cardiac and peripheral 4

Here, too, there is considerable overlap, primarily among the various veins of the periphery, where each leg may have different ones involved.

Discussion.

This is the first study of this kind made on the autopsy series at New Haven Hospital in at least twenty years. In general, the statistics reported above are in good agreement with those published by others from other centers (3-12). It is not the purpose of this part of the paper to determine

<u>why</u> these statistics show what they show, but to lay a basis for emphasizing the need for some definitive treatment of the patient who receives a major pulmonary embolus, and, in passing, to point out some other characteristics of pulmonary embolism as occurring in this series.

As mentioned elsewhere in this paper, ~~~~~~~ fatal pulmonary embolisms occurring on the medical services total more than all the other services put together. In agreement are Homans (3), who in 1947 reported 25% of the fatal pulmonary emboli in postoperative patients and 50% in medical patients, and Carlotti (4), who also in 1947 reported a ratio of 2.5 medical: 1 surgical. Homans (5) also noted that half of the cases of venous thrombosis result in pulmonary embolism, one-fifth of these in turn resulting in death due to pulmonary embolism.

Here we will not attempt to explain increase in fatal pulmonary embolism in the past three years. Although the incidence of <u>all</u> pulmonary emboli has not changed significantly in this time, the percentage of all pulmonary emboli resulting in death has increased remarkably, being 50% greater than the preceding 5-year period and 100% greater than the 5-year period preceding that.

As to be expected, the older age groups showed the greater proportion of embolic episodes, undoubtedly due to their poorer circulation overall.

Pulmonary embolism is one of the first diagnoses considered but one of the most difficult to prove. As seen in this series,

other diagnoses were made, without considering pulmonary
emboli, in over 64% of the cases. Nygaard (6) in 1938
reported an error in diagnosis in "from 33-89% (highest
in non-surgical cases)", a figure he quoted from Damblé
(7). Nygaard reviewed cases at the Mayo Clinic from
1921-1933 on the surgical service, reporting 239 cases of
pulmonary embolus, of which 224 cases were diagnosed
correctly. The most common incorrect diagnoses in his
series were cardiac failure and coronary occlusion,
indeterminate diagnosis, shock and hemorrhage, peritonitis,
pulmonary edema, coma, cerebrovascular accident, and other
conditions. Neuhof (8) in 1948 reported, of 83 cases, only
16 correct diagnoses and 13 in which pulmonary embolus
was considered, with 22 incorrect diagnoses and 37 in which
no impression was given. Louis Wolff (12) cites the
differential diagnosis as including angina pectoris, acute
myocardial infarction, pleurisy, pleurisy with effusion,
tuberculosis, pneumonia, acute heart failure, asthma, tumor,
central nervous system disease, and psychoneurosis.

In the diagnosis of thrombophlebitis Veal and Hussey
(13) reported calf tenderness in 96% of patients with the
condition, a positive Homan's sign in 92%, edema in 90%,
tachycardia in 21%, fever in 14%, with the first symptom of
pain in the leg in 75%. They noted pulmonary emboli in 20%
of their cases.

The therapy of thrombophlebitis in the fatal cases was
probably inadequate. None of them were on anticoagulant

therapy at the time of the embolic episode. Those who had
been on anticoagulants at one time for signs of thrombo-
phlebitis were taken off when the signs abated, but were
not treated again when signs returned. Proper use of
heparin etc. might have lowered the incidence significantly.
Santy (40) in 1949 reported 20 cases of attempted Trendelen-
berg Operations for massive pulmonary embolus from 1926 to
1939, but since the advent of heparin in 1939 reports only
2 cases.

The duration of life of the patient after the embolic
episode: in this series it is seen that almost 36% of the
patients died within 10 minutes of the onset, and 48% in
the first hour. Other authors have reported approximately
similar findings. Detakats, Beck, and Fenn (9) reported
in 1939 on 70 cases, in which 8.5% were found dead or died
in ten minutes, 31% died within 11-60 minutes, and 60.5%
after one hour; Neuhof (8) reported, of 83 cases, 20.5%
dying within 10 minutes, 31.8% within 11-60 minutes, and
47.7% after one hour; Griswold (10) reported 20 cases,
with 15% dying within 10 minutes, 55% in 11-60 minutes, and
30% after one hour; Nygaard (6) reported on 252, with 47.7%
dying within 10 minutes, 30.6% in 11-60 minutes, 21.4% after
one hour. Combining these figures:

                Total cases 492
                0-10 minutes 166 (33.7%)
                11-60 minutes 140 (28.4)
                more than 60 minutes . 186 (37.8%)

This is probably a valid distribution, involving a large
number of cases from 5 different series, so that were there
practical surgical therapy for pulmonary embolus it might
be theoretically possible to save more than 66% of these
patients, assuming suitable operative intervention could be
started within 10 minutes.

Although in all cases the terminal symptoms were not
described completely, it is worthwhile to see that the
frequency of symptoms is essentially the same as that
described by other authors. Dyspnea, cyanosis, rales,
fall in blood pressure with rise in pulse, respiration, and
temperature are commonly described as typical. De Takats
and Jesser (11) listed dyspnea, chest pain, cyanosis,
"weakness and rapid pulse", and fall in blood pressure.
Carlotti (4) listed rales, chest pain, fever, dyspnea,
tachypnea, dullness, and fall in blood pressure. In one of
the very finest discussions of pulmonary embolus Wolff (12)
reported chest pain in 75% (pleuritic in 50%, anginal in 24%),
dyspnea 50%, cough 35%, fever 67%, tachycardia 50%, pulmonary
signs (dullness, rales, etc.) in 60%.

In the present series 65% of patients dying of pulmonary
embolus had at least one embolic episode reported in the
chart or recognizable as suspicious from the description in
the chart before receiving the fatal embolus.

One of the most important findings from the study of the
postmortem cases is the site of lodgment of the pulmonary
embolus. Sixty-seven cases showed occlusion of a lobar or

largery pulmonary artery. Smaller emboli were not considered
the immediate cause of death although in some cases they
apparently were a major contributing cause. An embolus in
one of these larger vessels might be susceptible to removal
by surgery. Larger emboli of the so-called "massive"
proportion might also be removed by this procedure. In the
literature there are few classifications of similar data.
Crafoord and Benichoux (44) in 1952 found in 24 cases massive
pulmonary emboli in 2, right pulmonary artery emboli in 8,
left pulmonary artery emboli in 7, and main lobar artery
emboli in 7.

The Present Therapy of Pulmonary Embolism

1. Medical.

Modern medical therapy of pulmonary embolism revolves around the use of certain standard drugs which have been in vogue without much change for over twenty years. Therapy has been directed toward two aims particularly: toward relieving the anoxia attendant with blocking off a considerable portion of the functioning lung, and toward increasing the blood flow through the lung. The first is accomplished to a certain extent by giving the patient oxygen in high concentrations. Certain authors have stated that one of the prime reasons for fatality in cases particularly of massive pulmonary embolus has been the cerebral and cardiac anoxia and their complications (14). If what blood is flowing through the lung is as fully oxygenated as possible, this factor will be decreased maximally.

It is in the attempt to increase the blood flow that some authors think damage rather than help may be done. Papaverine and atropine are used with general accord because of their dilating effect on the pulmonary vasculature. Benk (15), Buck (16), DeTakats (17), and Collins (18) all have advocated the use of the former. Collins reported only three deaths in a series of twenty patients with pulmonary emboli treated with papaverine. Atropine has been suggested by Bardin (19) and is used here at New Haven Hospital.

Pressor drugs have been tried in attempts to increase

the pulmonary blood flow and keep the patient out of shock, Adrenalin will perform both functions well but puts a tremendous load on the right ventricle and so is considered unsatisfactory. Neosynephrine and ephedrine are not used because of the *same* ^reasoning (9).

Digitalis has been suggested but is considered inappropriate because of the increased load put on the right ventricle without lessening the peripheral resistance, and because some authors say it lowers the coronary blood flow (9).

Attempts to lower the pulmonary peripheral resistance with nitrates are unsatisfactory because of the concomittant fall in systemic blood pressure, lowered already by the embolization itself (9).

Venesection has been tried to decrease the blood volume and peripheral resistance but is of no avail if the right heart is already exhausted.

Finally, stellateganglion infiltration with procaine has been tried with fair results by Leriche et al. in Strasbourg (20).

In summary, medically the treatment of pulmonary embolus is oxygen to relieve the cyanosis, then papaverine or atropine to increase the pulmonary blood flow. Digitalis, adrenalin, etc. are not recommended strongly. Pain relief should be by drugs which do not depress the respiratory centers. Antibiotics would help control any infection which might otherwise develop. Blood transfusion should be given

for peripheral vascular collapse rather than pressor drugs.

2. Surgical.

From a surgical standpoint, treatment is more
specifically described, but with much poorer prognosis and
much more hazard. It has not changed at all in the past
46 years, ever since the original description of a surgical
operation to recover a massive pulmonary embolus was reported
by Trendelenberg in 1908 (21). Professor Frederick Trendelen-
berg in his original paper raised two questions which still
apply: "Whether the diagnosis can be ascertained with
sufficient accuracy, and whether there is sufficient time
for an operation." The first he answered in the affirmative,
citing as symptoms "pallor, sudden collapse, livid lips, loss
of pulse, deep and distressed respiration", particularly in
a postoperative patient. The second question he answered
with "maybe". In 9 cases he studied at Leipzig Hospital,
2 died within 10 minutes, and 7 lived 11-60 minutes.

He then described an operation exposing the pulmonary
artery through a T-shaped left-sided incision, making an
incision into the artery and removing the embolus with a
long pair of forceps, then closing the incision with clamps
to allow resumption of the flow of blood. Flow must be
re-established within 45 seconds or irreversible changes
would take place due to anoxia.

After a successful embolectomy on a calf, Trendelenberg
attempted two operations on humans without success. The

operation received a great deal of publicity and several
surgeons tried without success to revive patients until
finally in 1924 Kirschner (22) in Konigsberg had a survival.
He received plaudits from the whole world and Trendelenberg
himself presented him with a set of surgical instruments.
This success revived interest in the operation and many
surgeons again attempted the procedure. It was not until
February of 1927, however, that Meyer (23) succeeded at the
Krankhaus Westend in Berlin, using an anterior mediastinotomy
to avoid tearing into the pleural space. Following this,
there was another rash of attempts with several successful
results (24-32). In 1932 Eichelter (33) reviewed the
literature and found there had been 132 reported attempts
with only 9 successes. However, the operation by Lewis in
1939 was said by him to be the 12th success in the literature,
as well as the first in Great Britain (32).

The total number of attempts is not known at present;
surgeons seem to have given up reporting the failures.
Churchill (14) at the Massachusetts General Hospital reports
10 attempts with no survivors, but passes the following
comments on the procedure: opening the pleura is a mistake;
the preliminary incision can be done under local anesthesia
before clinical death; the Trendelenberg sound is too bulky
and should be replaced with a smaller one; intratracheal
oxygen under positive pressure is very valuable; and
suggests suction for the emboli that the forceps cannot reach
or engage. Shambaugh (34) in 1936 reporting from the Peter

Bent Brigham Hospital told of 4 trials in three years without success. Pilcher (35) in London reported doing 4 cases without success, stating that in two cases he felt in retrospect he had delayed too long; however, he feels a deliberate operation would have a greater chance of success.

In summary, a great number of attempts have been made with very poor results overall. Considering all the attempts reported above and all the successes known to this author, the mortality rate is 142/151 = 94%. The general attitude of the surgeons with any actual or literary experience with the Trendelenberg procedure may be summed up in Nygaard's observation: a "large part of the surgical profession may deem it unjustifiable" (6).

There have been very few modifications in the classic Trendelenberg operation since its invention. Instead of forceps Trendelenberg tried suction to remove the embolus but discarded the idea because he felt the intima would be injured and considered it unreliable. It was not used again until Nystrom (28) tried it on his first case after the forceps failed to deliver more than a few small clots. Suction engaged a large clot and retrieved it but forceps were finally necessary to remove it. In his paper he cites the dangers of exsanguination and air embolism in suctioning the pulmonary artery. He, too, used the classic one described in the original paper.

In 1944 Neuhof (42) described a transcardiac operation for the removal of a massive pulmonary embolus. In this

procedure he put hemostatic sutures into the right ventricle and introduced a #34 French catheter into the right ventricle, up the pulmonary trunk and applied suction. No clots were removed in several attempts and the incisions were closed. The patient died 15 minutes later. At autopsy thrombi were found in the right and left main pulmonary arteries about 2-3cm from the main trunk. He felt, although the operation was unsuccessful, that further attempts were justified.

No further attempts have been reported of an operation similar to Neuhof's up to this time.

The Experimental Work

Purpose.

The purpose of this experiment was to produce suitable emboli to the pulmonary system so as to simulate clinical pulmonary embolism, and to attempt via a transcardiac route the removal of such emboli by means of suction apparatus.

Material.

Ordinary laboratory dogs weighing 8-15 kilograms were used as experimental subjects. The usual table of instruments was used for making the abdominal and thoracic incisions, and the cannulations. In addition, a Bethune clamp was employed for cardiac hemostasis, suction being made through a #32 Bardex catheter with open end, collecting the material suctioned in a 500cc blood donor flask containing 15cc of citrate solution. Recordings of the arterial blood pressure were taken directly from the left femoral artery via a mercury manometer recording on an ordinary kymograph. Pressures in the right ventricle were recorded in a similar manner via a cardiac catheter placed via the right external jugular vein into the right ventricle under fluoroscopic and/or oscilliscopic control. In either case, a typical right ventricle pressure wave was obtained before finally tying the catheter secure. Fluorescin dye was used for the circulation times. EKGs were taken during the experiment by either a Simplescribe or Stethocardiette. To cannulate

the vena cava a long glass tube was used, ¼" in diameter
and about 24" long, bent slightly so as to permit resting the
tube at approximately a 30-degree angle.

Method.

Briefly, the experiment was designed so as to take
continuous arterial and venous blood pressure readings and
EKG before, during, and after the discharging of a large
blood clot into the inferior vena cava, and the production
with this clot of a massive pulmonary embolism. Before and
after the embolization circulation times would be taken.
In one dog after a suitable blood pressure change the chest
would be opened via a right-sided incision through the 4th
interspace and transcardiac suction with the Bardex catheter
instituted to retrieve the embolus. In the other dog the
clot was allowed to traverse the right heart and kill the
dog without intervention of any sort.

Procedure.

Under Dial anesthesia and with constant saline infusion
into the left antebrachial vein, the right external jugular
vein was exposed and a cardiac catheter introduced through it
into the right ventricle, position being checked with the
Hathaway pressure oscillometer until a typical right ventri-
cular tracing was obtained. Normal saline was slowly dripped
through the catheter after it was secured to prevent clogging.
The left femoral artery was then exposed and cannulated with

a 1/8" bore plastic cannula which was secured firmly also.
A bulldog serrefine clamp was placed proximal to the cannula,
to prevent clogging, until the readings were begun. By means
of three-way stopcocks both cannulations were connected by
water-tight systems containing dilute heparin solutions to
mercury manometers which recorded directly on the kymograph.

The inferior vena cava was then exposed through a right
lateral longitudinal incision, the peritoneum and contents
being retracted to expose the vessel from renal vein to
iliac bifurcation. Double ligation isolated about 2 inches
of vena cava which was then divided distally and cannulated
with the long glass tubing. This tubing was then rotated so
that blood flowed from the vena cava in to fill the tube with
about 45cc of blood. A rubber tube on the free end was then
clamped and the system so closed. The tube was then rotated
back so that it rested at about a 30-degree angle from the
horizontal and the blood in it allowed to clot. Two hours
were usually allowed for adequate clotting and clot retraction.

At the end of two hours the pressure systems were opened
to the kymograph and base line readings begun. Circulation
time was done with fluorecin from left antebrachial vein
to tongue. A baseline EKG was taken in the three limb
leads. A few seconds before the release of the clot the EKG
was turned on and a continuous reading on Lead I during the
embolization was obtained. The clamp on the tube was released
and the clot formed therein propelled into the venous system
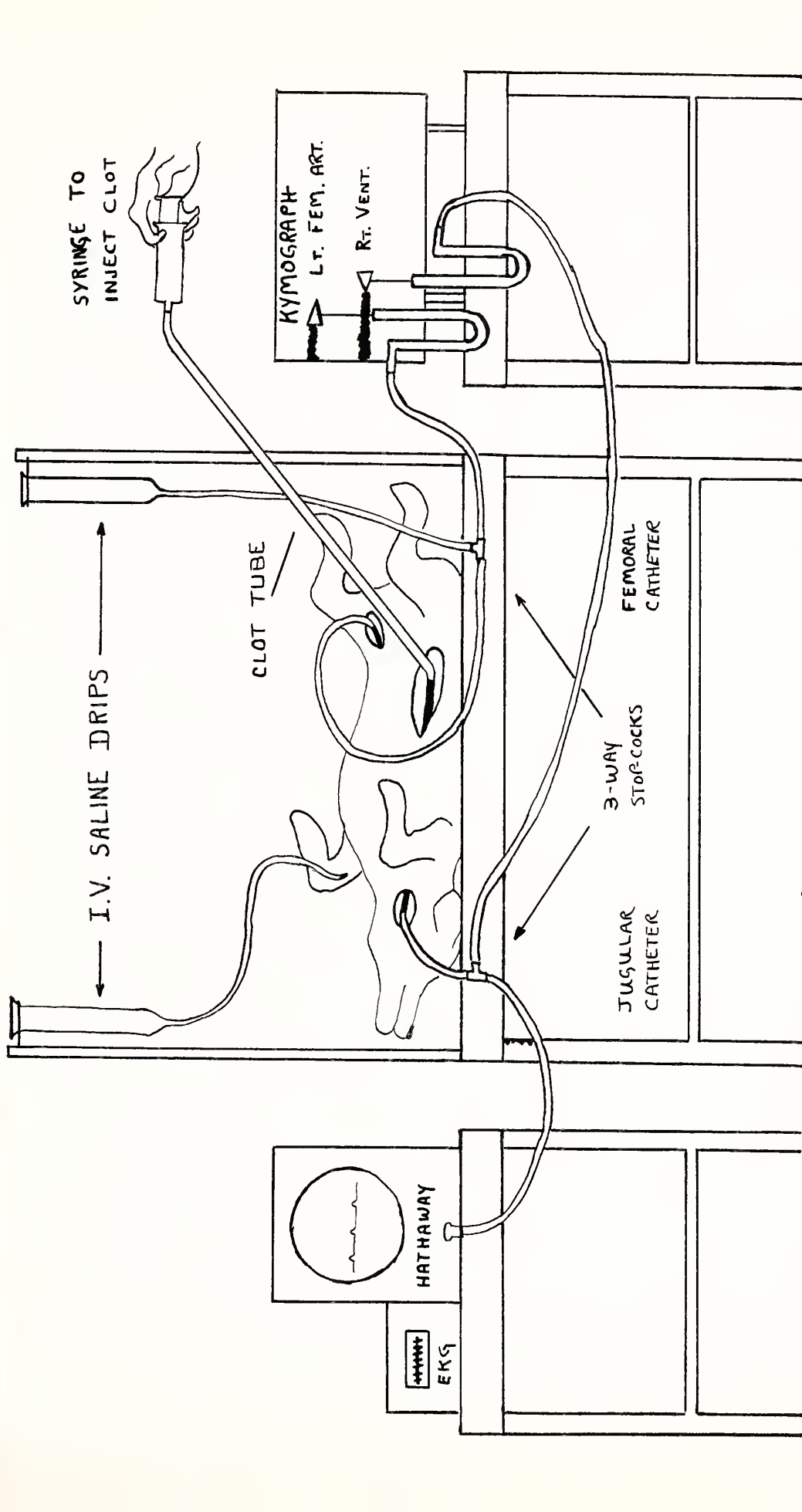with 50cc of normal saline. After the embolization   another

Diagram Showing Essential Features of Acute Preparation

circulation time was taken.

One dog was not interferred with and was allowed to die of his embolus. Another dog at this point had his right chest opened and the heart exposed through the right fourth interspace. The pericardium was opened and the right ventricle identified. Sutures were placed as in Figure 1. An incision was made between the sutures and the Bardex catheter introduced. Suction was applied intermittently as the catheter was introduced into the pulmonary arterial tree. The clots were collected in the citrated blood donor bottle. Each dog was sacrificed at this point and a postmortem done to determine the extent of embolization in the lungs remaining. A photograph of each heart-lung preparation was taken to record the findings.

Results.

The arterial and right ventricular pressures were plotted against time and these graphs may be seen on the following pages. Also included on the graphs are the essential points in the protocol.

In Experiment #1 an 8 kilogram dog was prepared as described and baseline readings were taken of the pressures. A circulation time was performed shortly before the graph begins and was reported as 51.7 seconds. This is extremely long and may be due to error in the placement of the needle in the vein. There was no chance for comparison after the
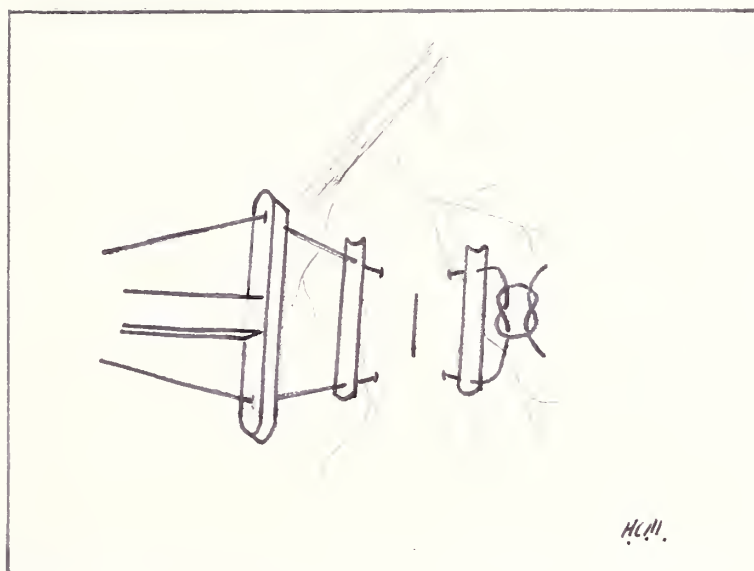
Figure 1.

embolus because the dog died within a few moments. EKGs
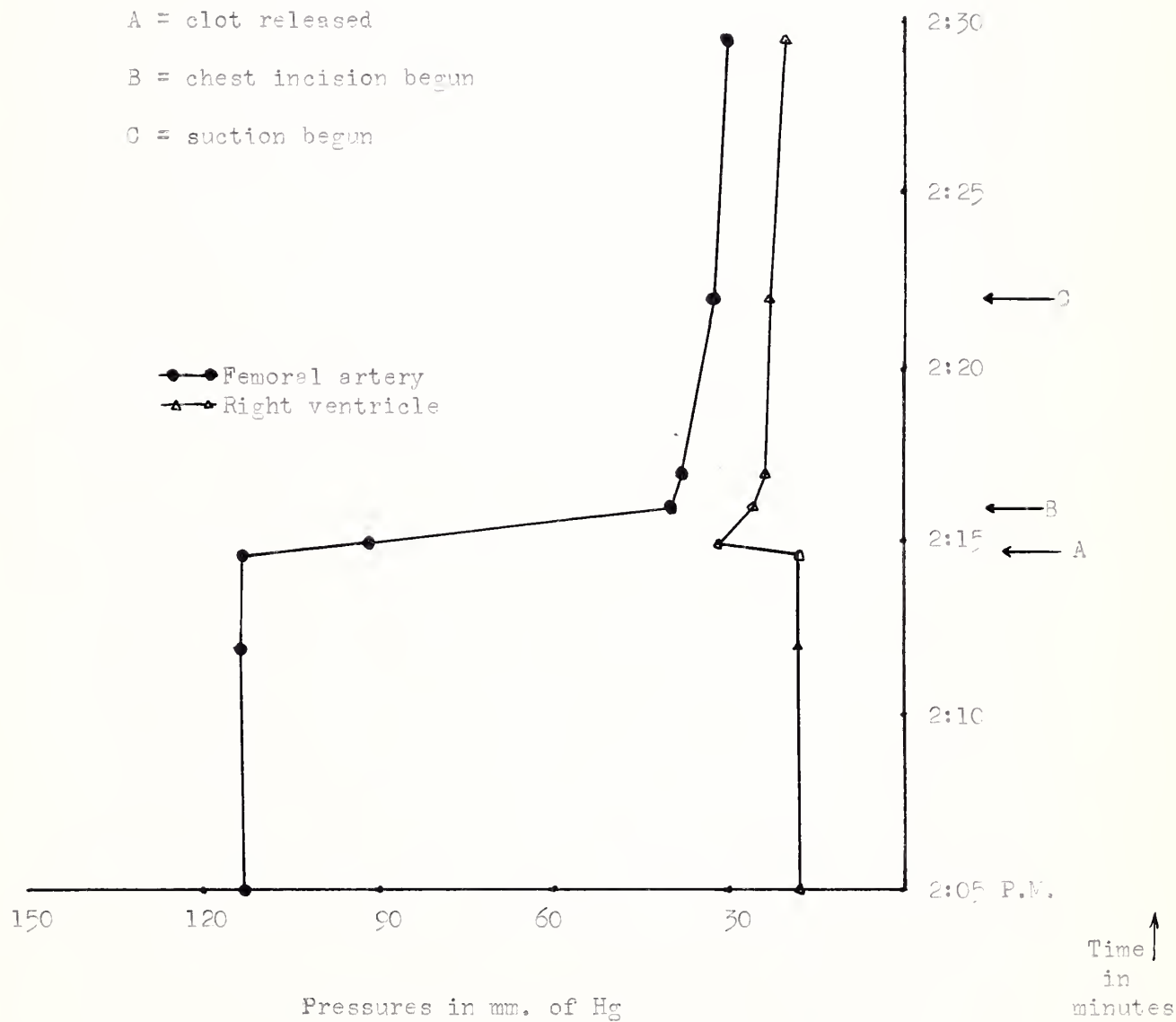were taken as described.

When it became evident that there were profound changes
in the pressure tracings on the kymograph, an attempt was
made to remove the clot. When the chest was opened, the
right auricle was seen to be turgid, cyanotic, and motion-
less; the right ventricle was similar and completely
without pulsation; the left ventricle was flaccid, pink, but
motionless. Suction was employed as described and large
amounts of clot were removed. In all, 20 grams of clot
were recovered from the citrated suction bottle. A total of
250cc of whole blood was removed also, none of which had
clotted. The quantity of clot released was measured and
found to be 40cc. Postmortem findings are seen in Photograph
#1. The illustration shows the heart and lungs with the
anterior wall of the right ventricle and auricle removed
and all the major pulmonary arteries opened. Arrows
identify portions of the clot. The clot is well-formed and
not fragmented remarkably. The clot has occluded all of the
pulmonary arteries, undoubtedly a "massive" pulmonary
embolus. The EKG record during the embolization was taken
in Lead I only and so no positive interpretation can be
made. Briefly though, signs of myocardial anoxia were
found: ST changes and the appearance of an S wave.

In Experiment #2, using a 15 kilogram dog, the usual
preparation was made. Circulation time before embolus was
9.75 seconds. EKG was taken for 10 minutes after embolization.

EKG taken from 2:14 to 2:17

Suction recovered 20.0 grams of clot
with 250cc. whole blood.

A = clot released

B = chest incision begun

C = suction begun

Femoral artery
Right ventricle

2:30

2:25

C

2:20

B

A

2:15

2:10

2:05 P.M.

150   120   90   60   30

Pressures in mm. of Hg

Time
in
minutes

DOG #1, March 31, 1954
8 Kilograms

RA

RV

Dog #1, 3/31/54

A = Fluorscin circulation time 9.75seconds.

B = clot released

C = Fluorescin circ. time 63.0seconds.

D = Artifical respiration started.

E = Heart stopped.

EKG taken from 12:42:30 to 12:53

●—● Femoral artery
△—△ Right ventricle

1:02 ←— E

12:57

12:52 ←— D

12:47

←— C

←— B

12:42

12:37

12:32 P.M.

←— A (11:55 A.M.)

11:02

10:57 A.M.

150   120   90   60   30   Time in minutes

Pressures in mm. of Hg

DOG #2, April 26, 1954
15 Kilograms
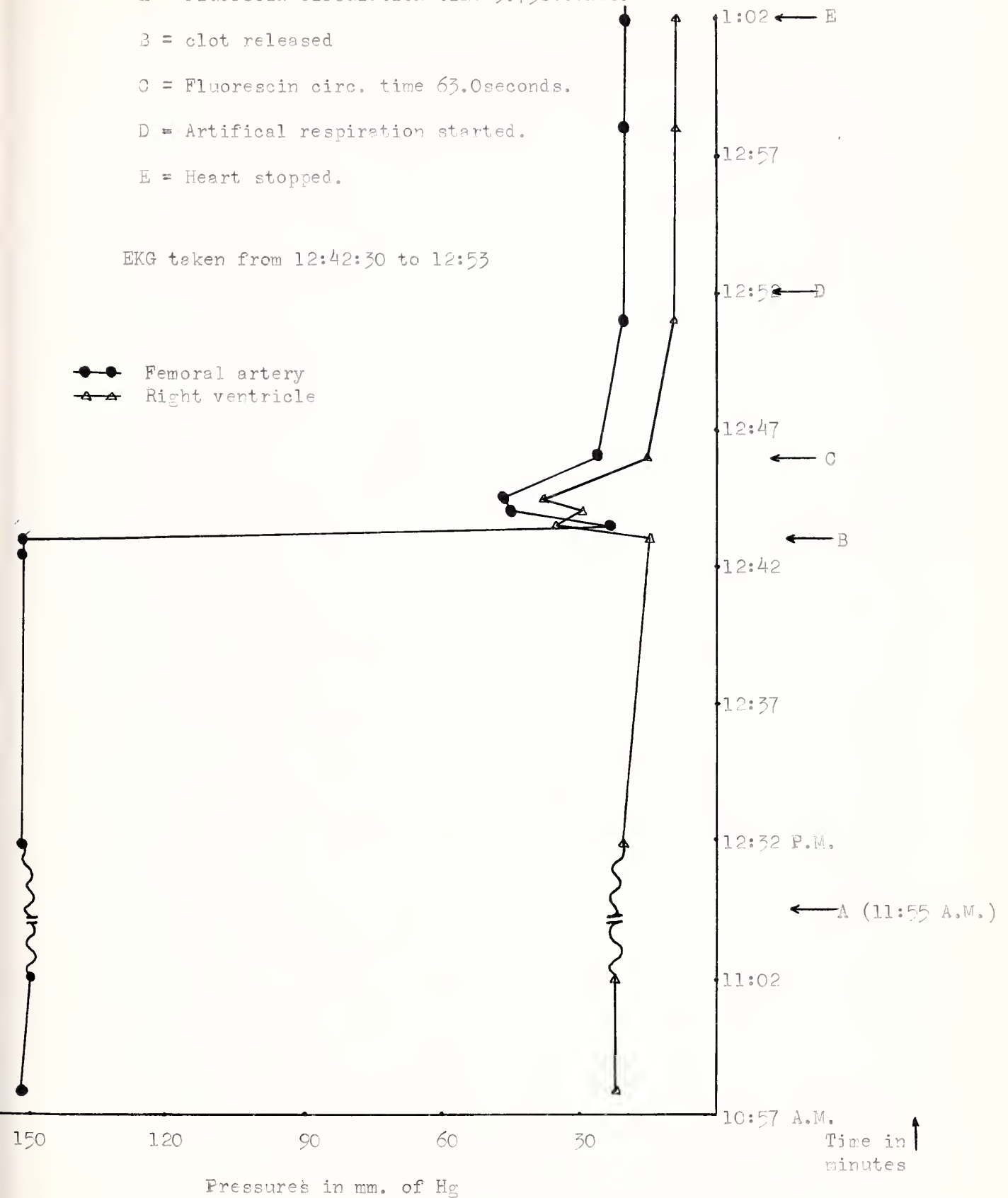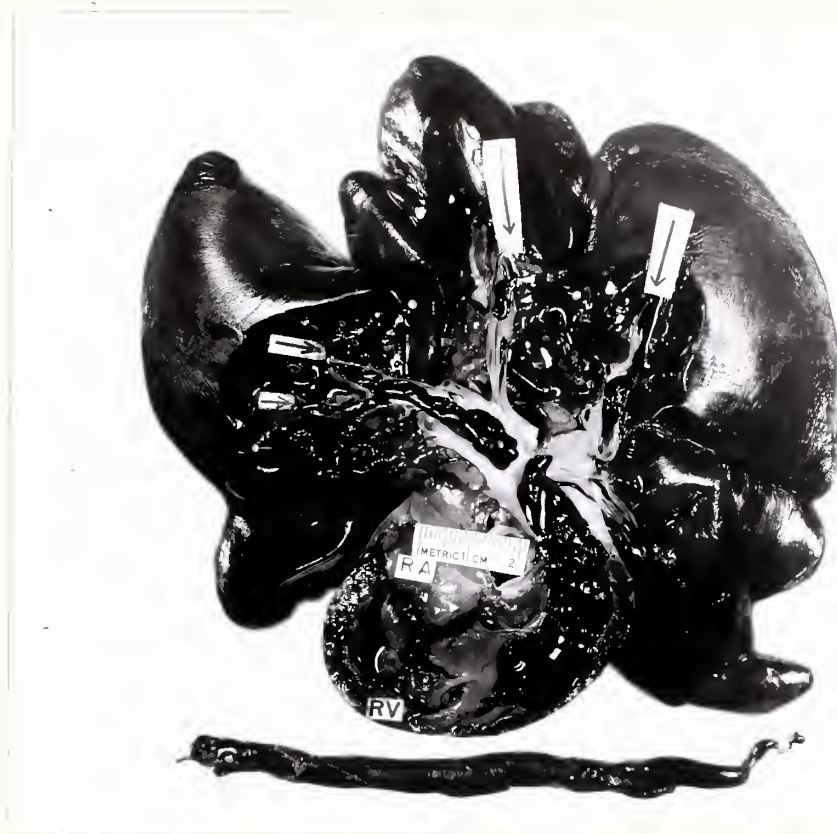
Clot below heart was removed from I. V. C. at postmortem.

Dog #2, 4/26/54

Upon release of the embolus, the respirations ceased abruptly and did not resume voluntarily. The blood pressure changes again were profound but no attempt was made to revive the dog, other than start artificial respiration. Circulation time done 3 minutes after embolus was 63.00 seconds. The heart continued to beat for 20 minutes after discharge of the embolus. At autopsy the findings were as seen in Photograph #2. EKG taken in Lead I only showed myocardial anoxia with abnormalities appearing in the conduction system. The quantity of clot discharged was 45cc.

Discussion.

There have been several attempts in the past to reproduce accurately pulmonary embolization. Many methods have been used, ranging from praffin "emboli" in various colors and sizes (36), to pieces of Penrose tubing filled with barium sulfate (37), to clots formed in the femoral veins and impregnated with barium sulfate (38), to clots of whole blood prepared in vitro in formalin and then injected via the jugular vein (39). Trendelenberg himself used pieces of calf lung introduced via the jugular vein (21). Blood clots were never used extensively because they tended to fragment into small pieces. Each method had its disadvantages, greatest of which was that none simulated the true picture of a clot traveling up from the leg veins to produce a massive pulmonary embolus with its secondary

blockage of the smaller arteries.

However, the work by Mendlowitz (37) in 1938 involved detailed studies of the circulatory changes following emboli. With his Penrose tubings he produced "saddle" emboli which obstructed at least one of the major pulmonary arteries. His studies showed that the pulse for from 3-30 minutes is grossly irregular due to auricular and ventricular premature systoles. The respirations gradually become deeper and more rapid. When the embolus enters the main trunk the pulse becomes more regular, rapid, and weak; the respirations become shallow and rapid, with gasping respirations appearing just prior to death. The cardiac output after embolus is decreased 50.4%, whereas the controls had a decrease of only 15.1%. The blood volume with embolus decreased 0.7%; with controls 3.2%. The embolus produced a decreased stroke volume, and increase in arterio-venous oxygen difference with severe arterial anoxemia, a fall in the mean arterial blood pressure which was slightly more than that of the controls, and a rise in venous blood pressure which was only slightly more than that of the controls. He reported no consistent changes in the circulation time with either but noted a moderate increase in the cyanide circulation time. There was no change in the rectal temperature, no variation in the plasma solids. The EKG showed generally an elevated ST segment in Leads II and III, similar to experimental coronary occlusion, with a left axis shift, the appearance of an S wave in II and III, and a diphasic QRS

complex.

Our studies involved no such elaborate computations or investigations. We measured only the arterial and right ventricular pressures, the circulation times, and the EKG. It was seen in these studies that we can produce a fatal pulmonary embolus very simply by this technique, suggested to me by Dr. W. W. L. Glenn. The size of the embolus is measurable, the character is such that it simulates the clinical embolus very closely, and the lethal quality can be made fairly constant. Emboli of this type lend themselves very well to studies of pulmonary embolic phenomena.

The changes in the blood pressure are consistent with those described by other investigators, but appear to be more profound than those found by Mendlowitz. Combined with the EKG changes presumably showing gradual cardiac anoxia and myocardial failure, it would seem to confirm the observations made by Churchill (14) in 1934 on the cause of death in massive pulmonary embolus. They are, that there is complete obstruction to the flow of blood through the pulmonary circulation with resultant anoxia to all parts of the body. The central nervous system and the myocardium being most sensitive to anoxia, there is cerebral and myocardial failure. With brain anoxia Churchill postulated failure of the respiratory center and cessation of voluntary breathing movements. The reason for the immediate stoppage of respiration is not quite clear, however, since it is so abrupt and follows the so-called "terminal gasp". The

primary factor would appear to be obstruction to the outflow
from the right heart, producing a diminished minute blood
flow with its secondary changes, the "hypokinetic circulatory
failure of Blalock", involving also cerebral and/or cardiac
anoxia with secondary acute heart failure due to decreased
cardiac output and decreased coronary artery oxygen
content. Churchill's listing of "immediate", "delayed",
and "late" deaths due to pulmonary embolism are convenient
divisions of this primary process and its sequelae.

The development of this technique of producing the
pulmonary embolus   provides a way of testing
practical means of removing pulmonary emboli, either .
medically or surgically. In this experiment the
uniformity of the reaction to the embolus makes it fairly
simple to evaluate the response of the dog to the surgery
done. While the results in the operative procedure used
here to remove the embolus are not consistent with
survival, this is probably not due to the failure of the
procedure itself. The heart had stopped before the suction
was begun and the myocardial anoxia probably militated
against revival. The removal of a good portion of the
embolus, however, makes it clear that the procedure is a
valuable one to develop further. It is plain from the
picture of the postmortem findings that a Trendelenberg
operation would probably have failed altogether. The
approach through the right ventricle permits removal of
emboli lying in that chamber or in the pulmonary outflow

tract.   In one recent Trendelenberg operation performed
in Lyons, France, in 1952 and reported in the literature
the operation was a failure due to the absence of the emboli
from the pulmonary~artery~.   On autopsy it was found in the right
heart itself.   The surgeon was able to identify the clot in
the right heart but felt that it was impossible to open
the chamber to retrieve it.   The patient succumbed three
hours later.

In addition, the approach through the right ventricle
would permit suctioning not only the right heart, but also
the pulmonary artery, its major branches, and the entrances,
at last, of the lobar arteries.   This would permit
theoretical therapy to cases similar to the 67 described
earlier in this paper.   The operation could be performed
under light anesthesia before the patient went into
extremis, and there need be no reason to delay the procedure
until the patient is clinically "dead", as in the
Trendelenberg operation.

Conclusions.

1. A simple method of producing a standard pulmonary
    embolus is described.

2. Pulmonary embolism in dogs results in acute fall in
    arterial blood pressure, rise in right ventricular
    blood pressure, prolongation of the fluorescin
    arm-to-tongue circulation time, and changes in the
    EKG suggestive of myocardial anoxia and failure.

3. A method of surgical removal of pulmonary embolus
    by means of transcardiac suction is described
    with excellent hemostasis achieved by means of
    the parallel bar technique with a modified Bethune
    clamp as previously described from this laboratory.

4. An attempted surgical embolectomy in the laboratory
    by this technique is reported as partially
    successful in the removal of the clots but
    unsuccessful in the revival of the dog.

5. This surgical procedure deserves further investi-
    gation, since it offers a good means of removing
    the clots before the patient is in extremis or
    clinically dead. It is entirely feasible, and
    would be recommended, to do the operation while
    the patient is still in fairly good condition.

General Discussion

As seen by the autopsy data, the problem of pulmonary embolism is still before us. It is hard to believe that the problem is becoming more serious but if statistics are believable, this would appear to be the case. The rate of fatal pulmonary embolus has increased a great deal in the past few years, even with the presence of anticoagulants in the armamentarium. And yet there have been no major advances in the therapy of the condition since the use of papaverine, atropine, and oxygen was started more than 20 years ago, or since the Trendelenberg operation was described 46 years ago. With the mortality of fatal pulmonary embolus being about 34% in the first 10 minutes, there would seem to be ample time for an operation on the remaining 66% before it was too late. In a patient who is in reasonably good condition the severity of the pulmonary embolism depends to a certain extent on the location of the embolus in the vascular tree. The rapidly fatal ones are usually ones which fall into the arbitrary classification "fatal", described in the first part of this paper. These are the ones which should be treated quickly and definitively.

At the present time the operative removal of pulmonary emboli is only rarely considered. The Trendelenberg procedure has a mortality rate above 94%. It is for this reason that we have explored the possibility of using the

transcardiac approach with removal of the emboli with suction.

The transcardiac operation should be considered seriously early in the stage of cardiac anoxia and exhaustion; it allows maximum opportunity for removal of the clots, there is no interruption of the flow of blood to the lung during the operation, and hemostasis is excellent.

Summary and Conclusions

1. A series of 290 fatal pulmonary emboli occurring in a group of 6529 consecutive autopsies at New Haven Hospital from 1935-1953 are reviewed.

2. A brief review of the medical and surgical therapy of pulmonary embolism is made.

3. A method of experimental production of a standard pulmonary embolus is described, with its effects in dogs on the arterial and right ventricular pressures, the circulation time, and the EKG.

4. An attempt in a dog to remove a massive pulmonary embolus by the transcardiac route is described.

References

1. Allen, E. V., Hines, E. A., Kwale, W. F., and Barker, N. W. Ann. Int. Med. 27:371, 1947.

2. Bauer, G. Heparin Therapy in a Deep Venous Thrombosis. J.A.M.A. 131:196, 1946.

3. Homans, J. Operative Treatment of Venous Thrombosis in the Lower Limbs. Am. J. Med. 3:345, 1947.

4. Carlotti, J., Hardy, I. B., Linton, R. R., White, P. D. Pulmonary Emboli in Medical Patients. J.A.M.A. 134: 1447, 1947.

5. Homans, J.   ibid.

6. Nygaard, K. K. Pulmonary Embolism: Considerations of Clinical Diagnosis and Possibilities for the Trendelen-berg Operation. Proc. Staff Meetings Mayo Clinic. 13: 586, 1938.

7. Damblé, quoted by Geissendörfer in Thrombose und Embolie. Leipzig, Barth, 1935, p. 159.

8. Neuhof, H. Venous Thrombosis and Pulmonary Embolism. p. 159, New York: Grune & Stratton, 1943. (Mt. Sinai Hosp. Monograph #2).

9. DeTakats, G., Beck, W. C., Fenn, G. K. Pulmonary Embolism: An Experimental and Clinical Study. Surgery, 6:339, 1939.

10. Griswold, R. A. in Ann. Surg., 93:33, 1933.

11. DeTakats, G., Jesser, J. H. Pulmonary Embolism: Suggestions for its Diagnosis, Prevention, and Management. J.A.M.A., 114:1415, 1940.

12. Wolff, L. Pulmonary Embolism. Circulation, 6:768, 1952.

13. Veal, J. R., Hussey, H. H. Surgery of Deep Venous Thrombosis of the Lower Extremity. Surgery 17:218, 1945.

14. Churchill, E. D. The Mechanism of Death in Massive Pulmonary Embolism. S., G., & O. 59:513, 1934.

15. Benk, W. Zur Behandlung der arterial Embolie. Munchen med. Wchnschr. 81:437, 1938.

16. Buck, W. Der unblutige Behandlung der Lungenembolie. Zentralbl. f. Chir. 65:140, 1938.

17. DeTakats, G. The Use of Papaverine in Acute Arterial Occlusion. J.A.M.A. 106:1003, 1936.

18. Collins, D. C. Pulmonary Embolism. Am. J. Surg. 33:210, 1936.

19. Bardin, P. L'Embolie pulmonaire. Paris: Masson et Cie, 1937.

20. Leriche, R., Fontaine, R., Friedmann, L. L'infiltration stellaire...dans l'embolie pulmonaire. J. chir. 50:737, 1937.

21. Trendelenberg, F. Ueber die operative Behandlung der Embolie der Lungenarterie. Arch. f. klin. Chir. 86:686, 1903.

22. Kirschner, M. in Arch. f. klin. Chir. 133:312, 1924.

23. Meyer, A. W. in Dtsch. z. Chir. 205:1, 1927.

24. Ibid. 211:352, 1928.

25. Crafoord, C. Two cases of Obstructive Pulmonary Embolus Successfully Operated Upon. Acta. Chir. Scand. 64:172, 1928.

26. Nystrom, G. Erfehren in drei nach Trendelenberg operierten Fallen von Lungenembolie. Acta. Chir. Scand. 64:110, 1928.

27. Meyer, A. W. Trendelenbergsche Lungembolie Operation. Med. Klinik. 24:1436, 1928.

28. Nystrom, G. Operation for Pulmonary Embolism. Ann. Surg. 92:498, 1930.

29. Meyer, A. W. Eine weitere (meine vierte) erfolgreiche Lungenembolieoperation. Dtsch. Z. Chir. 231:586, 1931.

30. Crafoord, C. in personal comminication cited by Lewis, (32).

31. Valdoni, P. Un caso di embolia dell'arteria polmonaire quarito con l'embolectomia. Policlinico (sez. prat.) 43:911-918, 1936.

32. Lewis, Ivor, Trendelenberg Operation for Pulmonary Embolism --a successful case. Lancet 1:1037, 1939.

33.   Eichelter, D. Die Operation der Lungenemboli nach
      Trendelenberg. Chirurgie. 4:209, 1932.

34.   Shambaugh, Philip. Pulmonary Embolectomy. Ann. Surg.
      104:5, 1936.

35.   Pilcher, R. Slowly Fatal Pulmonary Embolism. Lancet
      235:942, 1938.

36.   Mann, F. C. Pulmonary Embolus. J. Exp. Med. 26:337,
      1917.

37.   Mendlowitz, M. Experimental Pulmonary Embolism. Journal
      of Thoracic Surgery. 8:204-18, 1938.

38.   Martin, E. Uber experimental erzeugte Lungenembolie
      bei Hunden. Arch. f. klin. Chir. 155:577, 1929.

39.   Hall, G. E., Ettinger, G. H. An Experimental Study of
      Pulmonary Embolism. Canad. M. A. J. 28:357, 1933.

40.   Santy, P., Guillemin, G., Marion, P L'operation de
      Trendelenberg a-t-elle encore des indications? Lyon
      Chirurgical 47:850, 1952.

41.   Debakey, M. E. A Critical Evaluation of the Problem of
      Thromboembolism. International Abstracts of Surgery. 98.1, 1954.

42.   Neuhof, H. Problem of Emb. of the P. A.: Report of a
      Transcardiac Operation. Ann. Surg. 120:488, 1944.

43.   Snoke, Albert W. Personal communication.

44.   Crafoord, C., Benichoux, R. Le Traitment Chirurgical de
      l'embolie massive de l'artere pulmonaire. Revue Medicale
      de Nancy 77:523, 1952.

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